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Psychiatry Research 137 (2005) 161–174

PSYCHIATRY RESEARCH

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Cross-sex hormone treatment does not change sex-sensitive cognitive performance in gender identity disorder patients

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Received 6 January 2004; received in revised form 28 September 2004; accepted 28 May 2005

Abstract

Cognitive performance in untreated early onset gender identity disorder (GID) patients might correspond to their born sex and not to their perceived gender. As a current mode of intervention, cross-sex hormone treatment causes considerable physical changes in GID patients. We asked, as has been suggested, whether this treatment skews cognitive performance towards that of the acquired sex. Somatically healthy male and female early onset GID patients were neuropsychologically tested before, 3 and 12 months after initiating cross-sex hormone treatment, whereas untreated healthy subjects without GID served as controls (C). Performance was assessed by testing six cognitive abilities (perception, arithmetic, rotation, visualization, logic, and verbalization), and controlled for age, education, born sex, endocrine differences and treatment by means of repeated measures analysis of variance. GID patients and controls showed an identical time-dependent improvement in cognitive performance. The slopes were essentially parallel for males and females. There was no significant three-way interaction of born sex by group by time for the six investigated cognitive abilities. Only education and age significantly influenced this improvement. Despite the substantial somatic cross-sex changes in GID patients, no differential effect on cognition over time was found between C and GID participants. The cognitive performance of cross-sex hormone-treated GID patients was virtually identical to that of the control group. The documented test–retest effect should be taken into consideration when evaluating treatment effects generally in psychiatry.

Keywords: Gender identity disorder; Cognitive performance; Sex hormones; Longitudinal study

1. Introduction

Gender identity disorder (GID) in adults (DSM-IV 302.85; American Psychiatric Association, 1994) is characterized by a discrepancy between objective

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0165-1781/$ - see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.psychres.2005.05.014

born sex and subjective gender identification, expressed as a feeling of being born in the wrong sex. Although both biological and psychological models have been proposed (Baker, 1969; Hoenig and Kenna, 1974; Person and Ovesey, 1974a,b; Stoller, 1979, 1985; Person and Ovesey, 1983; Blanchard, 1989; Johnson and Hunt, 1990; Brems, 1993; Blanchard et al., 1995; Zhou et al., 1995; Cohen and Ruiter, 1997), there is no established aetiology for the GID syndrome (Cohen-Kettenis and Gooren, 1999; Michel et al., 2001). Regardless of etiological controversy, evidence has been presented that the cognitive performance of GID patients' might be skewed towards that of their subjective gender (Cohen-Kettenis et al., 1998). Such skewing might originate from prenatal or postnatal hormonal influences. In favor of the former, a prenatal organizational effect of sex hormones on cognitive performance in early onset GID patients has been postulated from studies of prenatal endocrine disorders such as congenital adrenal hyperplasia (CAH). In some of these studies, adolescent female CAH patients display a cognitive performance skewed towards that of healthy males. So far, enhanced spatial ability (Resnick et al., 1986), a lower verbal and performance IQ and lower perceptual speed scores (Nass and Baker, 1991; Hampson et al., 1998), as well as enhanced right hemisphere development (Nass et al., 1987; Kelso et al., 1999), have been described. These cognitive differences of female CAH patients would be hypothetically based on their androgenized prenatal and perinatal hormone profile, while their postnatal profile is normalized by corticosteroid therapy. On the other hand, several other studies have failed to verify differences in cognitive brain function of women with CAH compared with their healthy siblings (McGuire and Omenn, 1975; McGuire et al., 1975; Helleday et al., 1994; Kelso et al., 2000).

As a current mode of intervention in adult GID patients, cross-sex hormone treatment causes considerable somatic changes. In the course of such treatment, several authors have suggested that the cognitive brain function of adult early onset GID patients might be activated towards that of the subjective gender, thus paralleling the endocrine and somatic changes observed during treatment (Miles et al., 1998; Slabbekoorn et al., 1999; Van Goozen et al., 1994). Hence, androgen-treated female GID patients have been reported to improve in cognitive tasks generally favoring males ["mental rotation" (Van Goozen et al., 1994; Slabbekoorn et al., 1999)], but deteriorate in tasks favoring females ["verbal fluency" (Van Goozen et al., 1994)]. Conversely, male GID patients treated with estrogen reportedly showed a decrease in their performance on tasks favoring males ["mental rotation" (Slabbekoorn et al., 1999)], and an improvement in tasks favoring females ["verbal memory"(Miles et al., 1998)]. However, such an activating effect could not be replicated in a later study (Van Goozen et al., 2002).

The evidence for a hypothetically activating effect of cross-sex hormones in GID patients would appear to have support in cognitive studies of sex hormones substituted to elderly healthy males (Janowsky et al., 1994; Carlson et al., 1999; Maki et al., 2001), as well as postmenopausal women (Sherwin, 1988, 1997; Phillips and Sherwin, 1992; Yaffe et al., 2000) and female patients with dementia of the Alzheimer type (AD), in whom an improvement of cognitive performance has been reported (Henderson et al., 1996; Tang et al., 1996; Kawas et al., 1997). However, other studies of either healthy elderly females (Hackman and Galbraith, 1976; Ditkoff et al., 1991) or AD females have failed to observe such improvement (Henderson et al., 2000; Mulnard et al., 2000; Wang et al., 2000). Furthermore, some evidence for the activating hypothesis of cross-sex hormone is derived from studies of female cognitive function during different phases of their menstrual cycle (Hampson and Kimura, 1988; Saucier and Kimura, 1998), as well as from studies of testosterone fluctuations and their correlation to different cognitive functioning in men (Christiansen and Knussmann, 1987; Moffat and Hampson, 1996). However, other studies failed to support these observations (Gordon et al., 1986; McKeever et al., 1987).

The divergent results of the cognitive studies that address hormonal effects on brain function may be partly explained by the type of cognitive functions that were studied, the neuropsychological tests that were used, and the investigated confounders that were analyzed (e.g., education, health, mood) (Barrett-Connor and Kritz-Silverstein, 1993; McKeever, 1995; Teri et al., 1997; Wisniewski, 1998; Yaffe et al., 1998; Berenbaum, 2001; LeBlanc et al., 2001). For example, formal education and physical health status have been

found negatively correlated to the cognitive function of demented patients (Breteler et al., 1992; Keefover, 1996). Moreover, the statistically significant improvement over time in previous studies of retested patients may at least partly be related to the test/retest effect of repeated testing rather than to hormone administration (McCaffrey et al., 1993).

In addition to problems associated with methods of analysis, results can also be affected by differential sex-specific cellular responses to a given sex hormone. In other words, male and female cells may respond differently to a sex hormone depending on sex chromosome-encoded differences (Rimanoczy et al., 2001; Vathy, 2001). Furthermore, the possible estrogen-independent activation of intracellular estrogen receptors in brain tissue would make the aetiology of a hormone-responsive cognitive function even more complex (Ciana et al., 2003). Finally, the cognitive ability may also be influenced by an interplay between complex "biopsychosocial" factors and not only by sex (Breedlove, 1997).

We have recently described that the cognitive performance of young untreated early onset GID patients, before cross-sex hormone treatment corresponds to their born sex instead of their subjective gender (Haraldsen et al., 2003). Our data therefore did not support the recently published hypothesis of a differently organized cognitive function in early onset GID patients (Cohen-Kettenis et al., 1998; Van Goozen et al., 2002). The purpose of this study was to test whether cross-sex hormone treatment of early onset GID patients would shift their cognitive performance towards that of their subjective gender over a 1-year period of therapy.

2. Methods

2.1. Subjects

This study included 52 somatically healthy early onset GID patients who consecutively sought sex reassignment surgery (SRS) in Norway from 1996 to 1998 (GID-N, $n=33$, 21 females, 12 males, mean age=26.7, S.D.=5.9 years) or from the freestanding private Gender Center, Palo Alto, California, in 1997 and 1998 (GID-US, $n=19$, 9 females, 10 males, mean age=35.2, S.D.=10.0 years). All patients were evaluated according to the Harry Benjamin International Gender Dysphoria Association's Standards of Care (1990 and 1998; Levine et al., 1998). Furthermore, the patients underwent two independent comprehensive evaluations by two senior psychiatrists (one of them is the first author), who belong to the National Center of Expertise for evaluating GID patients. The National Center has existed for more than 40 years in Norway. In the US, the same procedure was used including the first author as one of the three evaluators. Disagreement between the evaluators regarding diagnosis led to exclusion of such patients from the study. All patients fulfilled the criteria for GID according to DSM-IV and the Swedish selection criteria for SRS (Wålinder et al., 1977). All included GID patients were diagnosed as early onset GID patients, fulfilling criteria A to D in DSM-IV from childhood on. They were either homosexually attracted by males or females ($n=38$), by both ($n=3$) or by neither ($n=9$) at the time point of investigation. Two patients reported heterosexual orientation.

All participants were Caucasians, chromosomally and endocrinologically screened, and free of medication. None of the GID patients had received previous cross-sex hormone treatment. Participants with any endocrinological, genetic, neurological or major psychiatric comorbidity were excluded [$n=3$, from GID-N (2 delusional disorders, 1 XXY anomalia)]. Furthermore, the control group members (C) were heterosexual Norwegian participants with no lifetime diagnosis of GID. They were either high school graduates, military recruits from the armed forces, college students or employees of the University of Oslo ($n=29$, 15 females; 14 males, mean age=24.3, S.D.=10.2 years). They were recruited by advertisement.

The age distribution in an independent sample t-test did not differ ($P=0.8$, mean difference=0.5 years) between females ($n=45$, mean age=28.4, S.D.=10.3 years) and males ($n=36$; mean age=27.9, S.D.=9.2 years). The age distribution was also equal between Control and GID-N groups ($P=0.5$, mean difference=1.55 years) but differed between Controls and the two GID groups ($P=0.04$, mean difference=−9.1 years) because of the older GID-US group.

The educational level of all participants (n=81) was scored and categorized as follows: 1=high school graduates ($n=27$), 2=college graduates ($n=43$),

3 = higher university degree ($n = 11$). Uncorrected one-way ANOVA revealed significant differences between all groups ($F = 71.9$, $P < 0.0005$). Thus, the lowest education level was found in the GID-N group (78.8% with only high school degree) and the highest level in the GID-US group (52.6% with university degree). There was no difference as to education between females and males in the groups (C: $F = 0$, $P = 1$; GID-N: $F = 1.6$, $P = 0.2$; GID-US: $F = 2.6$, $P = 0.1$), but a significant difference between males and females in the sample as a whole (men were more highly educated than females: $F = 5.7$, $P = 0.02$) when corrected for the significant influence of age on education ($F = 4.0$, $P = 0.03$). All participants in this study were right-handed.

2.2. Treatment

All born male GID patients ($n = 22$) received 50 μg of oral ethinylestradiol (Etifollin) daily during the first 3 months of treatment, and thereafter 100 μg daily. All born female GID patients ($n = 30$) received 180 mg testosterone enantate (Primoteston-Depot) as an intramuscular injection every third week.

2.3. Neuropsychological testing

Somatically healthy male and female GID patients ($n = 52$) were neuropsychologically tested 8 to 2 weeks before, and 3 and 12 months after initiating cross-sex hormone treatment, whereas untreated healthy male and female subjects without GID served as controls ($n = 29$). Each test session started at 09:00 h and lasted for 3 h with two 15-min breaks after the first and second hour. The order of test presentation was random and administered by one of two trained test assistants to all participants, including controls.

2.3.1. Neuropsychological tests

Six cognitive factors (rotation, visualization, perception, verbalization, logic, arithmetic) were examined by a selection of 11 tests in two parts from the officially distributed "Kit of factor-referenced cognitive tests" by ETS [Educational Testing Service (www.ets.org), licensing agreement signed 1996 (Ekstrom et al., 1976)], which is methodologically based on a factor analysis (Ekstrom et al., 1979). All cognitive factors were represented by four tests (two forms of a test in two versions) except perception (two tests). All the same tests were randomized and administrated on the two following sessions after 3 and 12 months of hormonal treatment. The tests were selected to represent cognitive factors, which reveal significant sex differences according to earlier studies (Van Goozen et al., 1994; Voyer et al., 1995; Cohen-Kettenis et al., 1998; Halpern, 2000). Thus, rotation and visualization were expected to favor males; perception and verbalization to favor females. Logic and arithmetic were expected to be neutral, not being associated with born sex, but instead with other predictors. Test instructions were given in each patient's mother language. All test sessions started at 09:00 h, stopped at 12:30 h, and included breaks.

Rotation was assessed by means of the card rotation test and the cube comparison test. In the former, the subject picks the one out of eight figures that represents a mirrored or rotated version of the stimulus figure. Three minutes are available for 10 exercises. In the latter test, a pair of imaged cubes, each with a different orientation, is determined to be identical or not. Three minutes are available for 21 exercises.

Visualization was assessed by means of the form board test and the paper folding test. In the former, a figure must be constructed by assembling up to five figures. Eight minutes are available for 24 exercises. In the latter test, a picture illustrates a folded piece of paper with a punched hole. Out of five additional pictures, the subject picks the one that represents the identical, but unfolded paper by determining the new position of the hole(s). Three minutes are allowed for 10 exercises.

Perception was assessed by means of the identical pictures test in which 48 figures are evaluated in 1.5 min. Out of five figures, the subject picks one that is identical to the stimulus figure.

Verbalization was assessed by means of the word ending test and the word beginning test. The subject writes as many words as possible with a given prefix or suffix within 3 min.

Logic was assessed by means of the nonsense test and the diagramming relationship test. In the former the subject is asked for the logical reasoning of two sentences that leads to the concluding third sentence. Four minutes are available for 15 exercises. In the

latter test, "Venn diagram" styled geometric figures represent the relationship between three words. Five different diagrams are presented for each exercise. Four minutes are available for 15 exercises.

Arithmetic was assessed by means of the arithmetic aptitude test and the arithmetic operation test. In the former, 15 min are available for 15 calculations. Results are picked from five alternative answers. In the latter test, 15 min are available for 15 calculations in which the subject picks the correct arithmetic operation required for a given result (e.g., addition, subtraction).

2.4. Laboratory methods

Blood samples were drawn during the second break at the first test session and for the GID-US and the GID-N participants at all test situations (e.g., before and after 3 and 12 months). All serum samples were stored at −20 °C until measured at the Hormone Laboratory, Aker University Hospital, Oslo. The blood samples obtained from the GID-US group were stored at −20 °C and kept frozen on dry ice during shipment to Norway, thus enabling identical analyses of all samples.

Serum concentrations of estradiol (E_2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), free thyroxine (FT_4), thyroid-stimulating hormone (TSH), and prolactin (PRL) were determined by time-resolved fluoroimmunoassays (Delfia, Wallac, Turku, Finland). Serum concentrations of cortisol, progesterone, sex hormone binding globulin (SHBG) and testosterone were determined by radioimmunoassays (Orion Diagnostica, Espoo, Finland), and so were dihydrotestosterone (DHT) and estrone (E_1) (in house radioimmunoassays).

The normal ranges for adults established in our laboratory were as follows: E2, males 0.08–0.11, females 0.08–0.85 nmol/l; FSH and LH, 1–12 IU/l; free T4, 8–20 pmol/l; TSH, 0.2–4.5 IU/l; PRL; 50–700 mIU/l; cortisol (08.00), 250–750 nmol/l; progesterone, males < 3, females in follicular phase < 3, in luteal phase > 15 nmol/l; SHBG, males 10–60, females 30–90 nmol/l; testosterone, males 8–35, females 0.3–2.8 nmol/l; DHT, males 1.40–2.60, females 0.35–1.00 nmol/l; and E1, males 0.10–0.28, females 0.11–0.45 nmol/l.

The free testosterone index (FTI) was calculated (testosterone / SHBG × 10) as an expression of the free and biologically active testosterone concentration. The normal ranges established in our laboratory ($n = 926$) were as follows: males 2.3–12.8, females 0.1–0.6.

2.5. Statistics

A series of the repeated measures ANOVAs (Altman, 1991; SPSS 11.0, 2001) were applied. The six measured cognitive abilities (perception, verbalization, arithmetic, visualization, logic, rotation) served as dependent variables. First, the time effect was evaluated. Next, each predictor's influence was analyzed [group (C, GID-N, GID-US); sex; age (years), and education level], and finally, each predictor's influence was adjusted for all others. All interactions were tested.

Pearson and Spearman correlations were calculated between the changes of the endocrine parameters (e.g., delta FTI, delta E2) and the changed neuropsychological test scores over time (Altman, 1991, SPSS 11.0). The significance level was 0.05. The assumptions of the analyses were checked and met.

Of 81 enrolled participants at baseline, 60 subjects were included in repeated measures ANOVA because of randomly missing values in 21 cases. Replacement of missing values could have reduced the variance and might have improved the chances of finding significant influences. There were no dropouts during the study. The calculated Greenhouse–Geisser Epsilon significance value is an adjustment used in repeated measures when the sphericity assumption is violated. Both numerator and denominator degrees of freedom must be multiplied by epsilon, and the significance of the F ratio evaluated with the new degrees of freedom. It tends to be an overly conservative estimate for relatively small sample sizes.

The study was approved by the Human Subjects Approval Board at Stanford University, Palo Alto, CA. It was also performed according to national legislation and institutional guidelines in Norway. All participants signed an informed consent form.

3. Results

3.1. Hormone analysis

In Table 1 the relevant endocrine data of GID patients and controls are summarized. No significant

Table 1
Biochemical characteristics of the study subjects

	GID						Controls	
	Females			Males			Females	Males
	T1*	T2*	T3*	T1*	T2*	T3*		
DHT ± (nM)	0.6 (0.4)**	1.2 (0.8)	1.8 (0.7)	1.3 (0.6)	0.8 (1.0)	0.6 (0.7)	0.4 (0.2)	1.3 (0.3)
E1 ± (nM)	0.4 (0.2)	0.4 (0.2)	0.3 (0.1)	0.3 (0.2)	0.6 (0.7)	0.6 (0.7)	0.3 (0.1)	0.2 (0.03)
E2 ± (nM)	0.4 (0.2)	0.2 (0.2)	0.2 (0.1)	0.1 (0.08)	0.2 (0.2)	0.2 (0.2)	0.3 (0.3)	0.1 (0.02)
FSH ± (IU/l)	8.0 (12.3)	7.1 (12.7)	4.7 (4.1)	4.7 (3.4)	2.2 (3.1)	1.7 (1.6)	7.5 (6.6)	3.7 (1.4)
LH ± (IU/l)	14.8 (15.5)	7.8 (11.1)	6.0 (6.3)	6.0 (3.3)	2.2 (1.8)	2.4 (2.7)	15.0 (23.7)	4.6 (1.6)
Progesterone ± (nM)	10.8 (15.5)	2.3 (5.1)	1.4 (1.4)	1.5 (0.6)	2.0 (3.0)	2.4 (3.6)	10.3 (20.7)	0.8 (0.4)
SHGB ± (nM)	48.1 (21.6)	27.6 (15.6)	26.3 (16.5)	32.4 (17.3)	151.9 (96.8)	189.8 (100.2)	75.6 (36.1)	23.8 (7.1)
Testosterone ± (nM)	3.2 (7.6)	23.3 (11.8)	29.2 (12.0)	16.8 (9.7)	9.0 (14.9)	6.8 (9.0)	1.2 (0.6)	17.4 (4.0)
FTI ± (T/SHBGx10)	0.7 (0.4)	8.4 (4.4)	11.1 (3.8)	5.2 (2.0)	0.6 (0.4)	0.4 (0.2)	0.2 (0.2)	7.3 (1.1)
Prolactin ± (nM)	219.0 (84.1)	220.5 (133.6)	194.2 (80.8)	174.3 (87.8)	213.2 (96.5)	212.3 (87.5)	251.9 (70.9)	142.8 (39.6)
Cortisol ± (nM)	348.4 (161.0)	288.0 (172.2)	301.2 (114.5)	473.9 (145.1)	648.0 (286.3)	629.3 (249.7)	316.6 (78.4)	196.3 (61.8)

T1* = baseline testing, T2* = after 3 months, T3* = after 12 months.
**Mean (± S.D.).
± Laboratory standard values; see Section 2.4 (Laboratory methods).

differences were found between the GID patients and their sex-matched controls before treatment, except for the male GID cortisol levels versus C, probably because of high prolactin as an expression of stress. Furthermore, the values were normal according to laboratory standards.

In male GID patients, ethinylestradiol treatment led to a significant decrease in testosterone levels and a 6-fold increase in SHBG levels, causing a reduction of FTI from normal male (5.2) to normal female values (0.4). Similarly, there was a 50% decrease in DHT. Only marginal increases were found in serum levels of E_1 and E_2, because the assays are specific for these two estrogens and do not detect etinylestradiol. However, the biological effect of the estrogen treatment was clearly demonstrated by the highly significant increase in serum SHBG levels in the male GID patients. In the female GID patients, testosterone treatment led to a significant increase in testosterone concentrations from normal female to normal male levels, and simultaneously to a pronounced reduction in SHBG levels. FTI increased 16-fold from normal female (0.6) to normal male values (11.1), and DHT showed a 3-fold increase.

The neuropsychological tests of the control and study female participants were planned to take place during the first 2 weeks of their cycle. The hormone measurements, however, showed that 8 of the 45 participating females were tested while they were in the luteal phase of their cycles (progesterone > 15 nmol/l). Nevertheless, the typical cognitive sex differences of GID patients were comparable to their sex control group at baseline, and are published elsewhere (Haraldsen et al., 2003). Male GID patients showed typical significant cognitive sex differences favoring them in rotation and visualization, and a tendency to perform more poorly in perception, compared with female GID patients. A similar cognitive sex-different pattern was shown for their control sex groups in this study.

3.2. Repeated measures

To test the hypothesis that cognitive performance would change over time, we first analyzed the neuropsychological data with regard to their temporal variation (Table 2). By means of repeated measures ANOVA, we found a highly significant improvement of performance over time for all cognitive factors (*P*-values T1 vs. T3 and *P*-values T2 *vs.* T3 as follows: perception $P = 0.0005$ and $P = 0.05$, arithmetic 0.0005 and 0.0005, visualization 0.01 and 0.0005, logic 0.0005 and 0.3, rotation 0.0005 and 0.03, verbalization 0.0005 and 0.2).

Second, to test the influence of each predictor (born sex, group, education, and age), we performed an unadjusted repeated measures ANOVA for each of them (Table 3). The main effect of the predictor age showed that younger subjects achieved significantly

Table 2
Raw scores of the tested cognitive abilities by group, time and sex

Cognitive factor	Group								
	C			GID-N			GID-US		
	T1* $n=29$	T2* $n=29$	T3* $n=29$	T1* $n=33$	T2* $n=33$	T3* $n=33$	T1* $n=19$	T2* $n=19$	T3* $n=19$
Perception									
Female $n=45$	41.2 (6.2)**	44.3 (3.3)	44.5 (2.2)	36.1 (8.1)	38.7 (6.2)	40.8 (7.1)	31.1 (8.7)	32.5 (8.1)	30.4 (7.2)
Male $n=36$	39.3 (4.4)	41.5 (5.2)	43.8 (3.7)	31.0 (6.0)	30.2 (6.6)	30.1 (4.7)	34.1 (7.9)	33.9 (7.4)	37.9 (7.9)
Arithmetic									
Female	5.1 (1.2)	5.2 (1.7)	5.6 (1.2)	4.1 (1.8)	4.4 (2.0)	5.0 (1.8)	6.9 (2.8)	7.0 (3.4)	7.6 (3.8)
Male	5.3 (4.4)	6.8 (1.5)	7.4 (1.2)	4.2 (1.2)	4.0 (1.2)	4.4 (1.2)	7.9 (2.50)	7.6 (2.1)	8.2 (2.9)
Visulaization									
Female	10.0 (3.4)	8.8 (2.1)	9.1 (2.5)	7.3 (4.5)	6.8 (3.3)	8.0 (3.7)	8.4 (3.9)	6.9 (2.2)	6.3 (2.6)
Male	11.4 (1.4)	9.8 (1.2)	11.4 (1.7)	8.8 (2.8)	6.9 (2.7)	8.4 (3.9)	12.4 (4.30)	9.8 (2.8)	11.0 (2.9)
Logic									
Female	6.5 (1.5)	6.9 (1.3)	7.0 (1.4)	5.8 (1.6)	6.5 (1.4)	6.5 (2.1)	7.2 (2.6)	8.0 (2.0)	7.7 (2.2)
Male	6.8 (3.4)	7.6 (2.0)	8.8 (2.3)	5.7 (1.5)	6.6 (2.0)	6.7 (1.3)	8.9 (2.3)	9.1 (2.2)	9.7 (2.5)
Rotation									
Females	3.8 (1.9)	7.8 (2.1)	9.2 (2.2)	3.6 (2.4)	8.7 (3.0)	8.5 (3.3)	3.7 (2.3)	6.8 (2.4)	6.8 (1.9)
Males	5.2 (1.8)	9.9 (1.2)	10.9 (1.8)	4.3 (1.7)	6.1 (3.1)	6.2 (3.00)	5.2 (1.3)	10.4 (2.5)	10.6 (2.8)
Verbalization									
Females	15.2 (3.4)	16.2 (2.0)	17.6 (3.3)	12.6 (5.7)	13.8 (5.4)	14.0 (6.5)	12.5 (4.7)	15.0 (1.3)	12.9 (5.0)
Males	15.2 (1.2)	19.2 (3.3)	21.0 (4.5)	1.9 (3.1)	13.9 (3.6)	13.1 (4.5)	14.1 (4.4)	14.4 (4.9)	15.1 (5.3)

T1*=baseline testing, T2*=after 3 months, T3*=after 12 months.
** Mean (±S.D.).

higher scores than older subjects (Table 3, background shadowed). None of the other unadjusted predictors influenced the main effect significantly (Table 3), but several significant interactions between time and predictor were found at this step of the analysis (sex × time, education × time, age × time, group × time; Table 3). There was no significant three-way interaction of born sex × group × time for the six investigated cognitive abilities (Table 3).

In the third and final step of the repeated measures ANOVA, the influence of all predictors' main effects controlled for the others and the interaction with time on the cognitive abilities was tested, as well as the controlled three-way interaction of born sex × group × time (Table 4). Only the main effect of age significantly influenced the test results. Higher age implied lower raw scores. In adjusted repeated testing, born sex, education and group showed no significant main influence. That means that in repeated neuropsychological testing, age will decide how well the participants will score on retesting. In contrast, the significant improvements (predictor × time interaction, Table 4) of the cognitive scores were verified in the final analysis for five of the six factors (perception, arithmetic, logic, rotation and verbalization). Only age and education were significantly associated with these improvements (except group and sex, which additionally influenced the improvements of the perception tests). Again, younger participants were better able to improve their scoring results over time than older participants. Participants with higher education level showed significantly better learning than lower educated ones. Only in perceptional tests, did GID-US and GID-N participants show a larger improvement than the C group, and females a larger improvement than males between test sessions 1 and 2. Nevertheless, this group differences were unidirectional, with positive improvements of the slopes in all three group categories (GID-US, GID-N, C). That means, there were qualitative differences in the improvements between groups and sexes. Overall, born sex and group (for 5 of 6 cognitive factors) were far away from any influence on the slopes. All interaction effects on all cognitive factors between time and these two predictors, which were significant when not adjusted for each other (Table 3), were completely eliminated after adjustment (except group × time and group û sex for perception; Table 4).

Table 3
Unadjusted repeated measures ANOVA of all participants ($n=81$)

		Perception	Arithmetic	Visualization	Logic	Rotation	Verbalization
Born sex	Mauchly's Test of Sphericity	0.95	0.95	0.72	0.98	0.79	0.94
	F, *df*, *P* (Main effect)	0.66; 1.91; 0.51	0.37; 1.90; 0.68	1.70; 1.44; 0.20	2.93; 1.95; 0.06	0.19; 1.65; 0.80	0.47; 1.83; 0.61
	F, *df*, *P* (predictor × time)	4.49; 1.00; 0.04[a]	2.10; 1.00; 0.15	3.03; 1.00; 0.09	3.17; 1.00; 0.08	1.33; 1.00; 0.26	0.15; 1.00; 0.70
Education[b]	Mauchly's Test of Sphericity	0.96	0.94	0.76	0.97	0.82	0.90
	F, *df*, *P* (Main effect)	0.53; 3.84; 0.71	0.97; 3.77; 0.42	2.61; 3.00; 0.06	0.45; 3.89; 0.80	1.40; 3.27; 0.25	1.62; 3.60; 0.18
	F, *df*, *P* (predictor × time)	0.98; 2.00; 0.40	18.4; 2.00; <0.0005[a]	4.92; 2.00; 0.01[a]	16.5; 2.00; <0.0005[a]	2.88; 2.00;0.07	12.1; 2.00; <0.0005[a]
Age[c]	Mauchly's Test of Sphericity	0.96	0.96	0.77	1.0	0.83	0.86
	F, *df*, *P* (Main effect)	3.53; 1.92; 0.03[a]	3.35; 1.92; 0.04[a]	3.51; 1.53; 0.05[a]	0.45; 1.9; 0.63	2.52; 1. 66; 0.10	4.63; 1.71; 0.02[a]
	F, *df*, *P* (predictor × time)	8.4; 1.00; 0.005[a]	15.2; 1.00; 0.0005[a]	0.26; 1.00; 0.61	4.90; 1.00; 0.03[a]	3.63; 1.00; 0.06	0.08; 1.00; 0.77
Group[b]	Mauchly's Test of Sphericity	0.96	0.96	0.75	0.97	0.82	0.91
	F, *df*, *P* (Main effect)	0.62; 3.85; 0.70	0.78; 3.82; 0.53	1.29; 3.00; 0.3	0.40; 3.90; 0.80	1.74; 3.27; 0.16	1,96; 3,.62; 0.11
Born sex × group × time interaction	*F*, *df*, *P* (predictor × time)	10.8; 2.00; <0.000[a]	14.7; 2.00; <0.0005[a]	3.72; 2.00; 0.03[a]	8.42; 2.00; 0.01[a]	1.25; 2.00; 0.30	5.67; 2.00; 0.006[a]
	F, *df*, *P*	2,24; 3,72; 0,07	1.58; 3.89; 0.19	1.90; 2.90; 0.14	0.57; 3.90; 0.68	0.90; 1.61; 0.39	0.55; 3.60; 0.67

Unadjusted *P*-values for each predictor's influence are given for the six cognitive abilities in the 'Main effect' lines.
The 'predictor × time' lines apply to interactions. For instance, the *P*-value for born sex is 0.51 for perception, while the interaction of born sex×time is significant (*P*-value 0.04).
The analysis is based on repeated measures ANOVA with Greenhouse–Geisser correction.

Table 4
Adjusted repeated measures ANOVA of all participants ($n=81$)

		MS**	Born sex	Education	Age^{++}	Group^{+}	Group × sex × time interaction
Perception	*F*, *df*, *P* (Main effect)	0.95	0.44; 1.90; 0.63	0.77; 3.81; 0.54	2.87; 1.97; 0.06	0.85; 3.81; 0.94	
	F, *df*, *P* (predictor × time controlled)		9.54; 1.00; 0.003***	7.60; 2.00; 0.001***	6.50; 1.00; 0.014***	12.70; 2.00; <0.005***	1.29; 7.39; 0.26
Arithmetic	*F*, *df*, *P* (Main effect)	0.92	0.45; 1.92; 0.61	2.15; 3.85; 0.08	2.95; 1.92; 0.06	1.13; 3.85; 0.35	
	F, *df*, *P* (predictor × time controlled)		0.37; 1.00; 0.55	3.87; 2.00; 0.03	9.10; 1.00; 0.004***	0.85; 2.00; 0.43	1.25; 7.80; 0.28
Visualization	*F*, *df*, *P* (Main effect)	0.72	2.07; 1.44; 0.15	1.57; 2.88; 0.21;	2.04; 1.40; 0.15	0.61; 2.88; 0.61	
	F, *df*, *P* (predictor × time controlled)		1.65; 1.00; 0.21	2.68; 2.00; 0.08	0.75; 100; 0.39	1.50; 2.00; 0.23	0,91; 2.92; 0.44
Logic	*F*, *df*, *P* (Main effect)	0.97	2.59; 1.94; 0.08	0.10; 3.88; 1.00	0.86; 1.94; 0.42	0.09; 3.80; 0.98	
	F, *df*, *P* (predictor × time controlled)		0.88; 1.00; 0.35	5.62; 2.00; 0.006***	1.12; 1.00; 0.28	0.43; 2.00; 0.65	0.59; 3.9; 0.66
Rotation	*F*, *df*, *P* (Main effect)	0.84	0.62; 1.67; 0.51	0.85; 3.34; 0.48	2.78; 1.67; 0.08	0.60; 3.34; 0.67	
	F, *df*, *P* (predictor × time controlled)		0.41; 1.00; 0.53	3.25; 2.00; 0.05***	6.0; 1.00; 0.02***	0.58; 2.00; 0.57	1.15; 3.29; 0.34
Verbalization	*F*, *df*, *P* (Main effect)	0.85	0.59; 1.7; 0.53	0.27; 3.40; 0.90	3.7; 1.70; 0.03;***	0.63; 3.40; 0.60	
	F, *df*, *P* (predictor × time controlled)		0.05; 1.00; 0.82	6.5; 2.00; 0.003***	1.04; 1.00; 0.31	1.63; 2.00; 0.21	0.27; 3.40; 0.87

**Mauchly's Test of Sphericity.
***Statistically significant differences.
$^{+}$Sex, Education (high school, college and university degree), and Group (C, GID-N and GID-US) used as contrasted factors.
$^{++}$Age continually distributed, used as covariate; each predictor is controlled for the others.
Adjusted *P*-values for each predictor's influence are given for the six cognitive abilities in the 'Main effect' lines controlled for the others. The 'Predictor × time' lines apply to interactions. For instance, the *P*-value for born sex is 0.63 for perception while the interaction of born sex × time is significant (*P*-value 0.003).
The analysis is based on repeated measures ANOVA with Greenhouse–Geisser correction.
Used model (Predictors: fixed factor born sex; group, education; as covariate served age. All controlled for each other. As dependent served each cognitive factor).

3.3. Hormonal and cognitive changes over time

In the fourth step of data analysis, we investigated the relationship between hormone serum levels and cognition. There were no significant Pearson correlations between any of the endocrinological parameters (e.g., Delta LH, FSH) and the change of any of the neuropsychological test results (e.g., for example Pearson correlation for rotation = 0.11, $P=0.54$). Plasma hormone levels may not be normally distributed (although in our study the assumptions of normality of all delta values were not rejected). Therefore, we also performed Spearman correlations, but the results did not differ.

The "male" and "female" cognitive factors showed a development similar to the sex-insensitive "control" cognitive factors, despite different gender identifications or sex. Instead, only age significantly influenced the main performance of the repeatedly tested cognitive function. Furthermore, age and education significantly predicted the learning ability of the participant.

4. Discussion

In our recently published analysis of untreated healthy early onset GID patients, we showed that born sex predicts the cognitive pattern of GID patients and that of their born sex control group in a similar fashion (Haraldsen et al., 2003). Despite their different gender identity, all male participants scored significantly higher in rotation and visualization than females. Although a significant female advantage in verbal fluency and perception was not verified, a tendency could be documented for the latter.

In the present study we show that cross-sex hormone treatment also fails to change cognitive function

in early onset GID patients. The cognitive ability remained similar to that of their born sex control group, a finding that is in strong contrast to the somatic and endocrine changes observed with such treatment. Instead, we demonstrated a positive, unidirectional learning effect in all participants that we interpret as a test/retest effect. During 1 year of cross-sex hormone treatment, all group categories (GID-N, GID-US, C) and both sexes showed a parallel improvement of their test scores (Table 4). There was no significant three-way interaction of born sex × group × time for the six investigated cognitive abilities (Tables 3 and 4). That implies, for instance, that a potential interaction between group and time does not depend significantly on sex. Our data demonstrate that the slope of the learning curve depended significantly on the interaction between time and age, as well as between time and education level. All other predictors had a parallel impact on the overall unidirectional, positive test score improvements (Table 4). Younger and higher educated participants "learned better" than older participants. Our findings therefore fail to support two of the few earlier publications in this field (Van Goozen et al., 1994; Slabbekoorn et al., 1999), which reported an increase of the mental rotation factor scores over time, explained by cross-sex hormone treatment. In addition, one of these studies (Van Goozen et al., 1994) showed deteriorated verbal fluency scores in female GID patients treated with androgens. We were unable to replicate any of these results. Furthermore, our results contradict findings of a negative "short-term" influence on spatial abilities over a 3-month period in estrogen-treated male GID patients (Slabbekoorn et al., 1999). On the other hand, we partly confirm two earlier studies, which showed no effect of estrogen treatment on spatial ability in male GID patients (Miles et al., 1998; Van Goozen et al., 2002) and no effect of testosterone treatment in female GID (Van Goozen et al., 2002). Miles et al. (1998) also assessed estrogen sensitivity by showing an effect on verbal memory in male GID patients treated with estrogens. We used a different verbalization test to assess estrogen sensitivity (verbal fluency), which did not permit direct comparison.

The different results might be partly explained by the chosen statistical approach. To specify the effects of various possible confounders (age, born sex, education, endocrine changes) on repeated neuropsychological testing in GID patients, we took advantage of recruiting young subjects from a homogenous public health care system (GID-N) and older subjects from a private, insurance company financed health care system, the latter also having a higher mean socioeconomic status (GID-US). Although a confounder does not show a significant correlation with the test result, it might be identified as significant in later analysis in combination with other confounders (Altman, 1991). We therefore included all variables of interest in the final analysis. Interestingly, although we observed *group* × *time* interactions in the second step of analysis (confirming the hypothesis of a different slope between the groups based on endocrine changes, Table 3), no *born sex* × *group* × *time* effects were found (Table 3). Moreover, these significant differences disappeared in the final adjusted analysis (Table 4). Moreover, group differences were only seen in the variable perception, but no interaction was found between *group* × *time* or *group* × *sex* × *time* for any of the cognitive factors. This means that the same kind of movement with time (a unidirectional improvement of the slope) was found in all groups and both sexes. Further, it could be argued that the two different GID groups do not belong to the same diagnostic groups. However, all included GID patients fulfilled early onset GID criteria and were almost all homosexually orientated.

Furthermore, in the earlier studies, the endocrine changes were not monitored by serum samples. This is an advantage of the present study. Here, we were unable to find any correlations between the significant endocrine changes and the improved test results (e.g., Delta Rotation versus Delta Testosterone). Although the test/retest effect observed in our study was significant, it was relatively small and unlikely to conceal any substantial effect of the treatment. Given a commonly used significance level of 5% and a power of 80% (using rotation as an example), we calculated that 30 individuals in each sex group are sufficient to detect a standardized clinical difference of 0.74 [the figure actually observed at baseline, Table 2 (Altman, 1991)]. The sample size in our study exceeds this requirement. Moreover, repeated measurement also adds to the power.

Although our present study had the power to register sex and group differences, as well as a potential crossover phenomenon, it could be argued that our

female cognitive factors did not show significant differences at baseline (except a tendency for perception) and therefore might be insensitive to "cross-sex changes". Nevertheless, such a cross-sex phenomenon has been reported without documenting significant sex differences at baseline (Van Goozen et al., 1995; Slabbekoorn et al., 1999).

Interactions between *sex and group* were not seen in our baseline study (Haraldsen et al., 2003). In addition, in the present study no temporal interactions could be found between *sex, group and time* for the investigated cognitive factors with help of the Repeated Measures General Linear Model. However, the significant influence of born sex at baseline on some cognitive factors might have been missed in repeated measurements because of the strong and similar influence of age in both sexes on the learning effect, as well as the strong influence of age as a main effect on repeatedly measured cognitive functions. Nevertheless, we documented only a unidirectional tendency of the differences between the sexes (Table 2) and documented no *cross-over* phenomenon which would have given significant results in the adjusted repeated measures ANOVA of *group* × *time* or *group, sex and time* (Table 4). This result is supported by the absence of a correlation between hormonal and cognitive change (see p. 13).

Our findings are in line with the negative studies of patients receiving hormone replacement therapy in deficiency states or of patients with prenatal endocrinological diseases (Wisniewski, 1998; LeBlanc et al., 2001). Despite the methodological problems in repeated measures studies of cognitive function, prenatally or postnatally imprinted target cells are re-influenced by their cognate ligand (McEwen, 1997; McEwen et al., 1997). In cross-sex hormone treatment, however, the sex hormones act on target cells that have not been previously exposed to such high levels of these hormones. Furthermore, cross-sex testosterone treatment probably increases aromatization of testosterone to estrogen, and this may cause even higher estrogen levels in the brains of biological females (Krey et al., 1982; Westley and Salaman, 1977). Moreover, sexually differentiated regions and target cells may interact in a complex fashion with sex steroids to maintain sexually dimorphic peptide expression, in which case cross-sex hormones treatment would not necessarily result in a unidirectional "cross-sex cognitive performance".

In conclusion, this study provides strong evidence that the cognitive performance of healthy GID patients is resistant to cross-sex hormone treatment, and is therefore in strong contrast to the substantial peripheral effects of this treatment. Taken together, our previous (Haraldsen et al., 2003) and the present study show that early onset GID patients possess not only the cognitive performance pattern of their born sex before treatment, but their cognitive pattern is also resistant to the impact of cross-sex hormones. In other words, our study failed to support previous studies and provided no evidence for the role of cross-sex hormone treatment in the malleability of adult cognitive brain function. In addition, the documented test/retest effect is of tremendous importance for cognitive research for all patient groups and should be taken into consideration when evaluating treatment effects generally in psychiatry.

Acknowledgments

The study was supported by the Norwegian Research Council; the Independent Order of Odd-Fellows; the Andresen foundation grant; the University of Oslo; and Stanford University. The authors thank Liv Helgaker for test and secretarial assistance, the technical assistants of the Hormone Laboratory of Aker University Hospital, the official group for the evaluation of GID patients in Norway, Regina Casper, Alan Schatzberg, Donald Laub, Judy van Maasdam and Guttorm Haraldsen for assistance and helpful discussions, and all participants.

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